PRIORITY:

Improving Disease Outcomes for HIV-Infected Individuals

Drug Discovery, Development, and Treatment

Research Toward a Cure

AREA OF EMPHASIS

Drug Discovery, Development, and Treatment

FY 2015 RESEARCH PRIORITIES

- Accelerate the discovery and validation of strategies, targeting new and existing viral and cellular targets that provide safe, tolerable, maximally long-term suppressive antiviral activity.
- Advance the discovery and validation of therapeutic strategies to prevent progression of HIV and its associated comorbidities, including inflammation, coinfections, and other clinical complications across the lifespan of HIV-infected individuals.
- Support research on the mechanisms of HIV persistence and develop strategies to prevent the establishment of, decrease, or eliminate viral reservoirs that persist despite optimal antiretroviral (ARV) treatment.
- Develop and evaluate methods, tools, and intervention strategies that improve entry into, and retention in, HIV care.
- Develop and test strategies to improve adherence to ARV drug regimens and regimens to prevent and treat HIV-associated comorbidities used for treatment and prevention in domestic and international settings.

OBJECTIVE–A: Discover and Develop Anti-HIV Treatments

Identify and validate viral and host cellular functions required for HIV replication that can be targeted for viral inhibition, eradication of persistent virus, and prevention of transmission. Discover and develop novel agents and therapeutic strategies that have enhanced half-life and tissue penetration, as well as therapeutic strategies that are effective against drug-resistant virus. Encourage collaborations among academia, industry, private and public organizations, the community, and the NIH.

STRATEGIES

- Identify, characterize, and validate viral and host targets for anti-HIV therapy. Develop predictive test models, including appropriate lentivirus animal models, to aid in identifying agents and strategies active against these targets.
  - Identify the cellular reservoirs of latent HIV *in vivo* and develop physiologically relevant *in vitro* and *ex vivo* organ or tissue models that can be used to discover agents or approaches that target and eliminate reservoirs.
  - Develop new agents and treatment strategies that target, inhibit, and clear HIV in cellular, anatomical, and organ reservoirs and sanctuaries, including agents that can suppress or eradicate HIV in non-T-cell reservoirs.
  - Characterize novel antiviral agents with respect to their preclinical, immunologic, pharmacokinetic (PK), pharmacodynamic (PD), toxicity, and teratogenicity profiles.
  - Develop new drugs, biologics, extended-release formulations, and routes of administration to increase safety, tolerability, durability, and ease of use of therapeutic agents.
  - Employ whole animal and *ex vivo* organ or tissue models of lentivirus infections to study the biologic and pharmacologic characteristics of therapeutic agents.
  - Acquire structural information on HIV, including the RNA genome, and cell constituents involved in HIV infection and replication for the design of therapeutic agents and therapeutic vaccine candidates with improved potency and selectivity. Post lead structures on publicly available databases.
  - Support genome-wide association studies and integrate systems biology approaches, including genomics and informatics paradigms, concepts, and methodologies, into mainstream drug discovery and development of therapeutic entities and strategies.
  - Develop enabling, rapid, and high-throughput technologies to accelerate and optimize the discovery and development of therapeutic entities and strategies; expand the infrastructure to provide services and reagents needed by the scientific community.
  - Evaluate the intracellular PK and activity of ARV agents in different cell types, different stages of the cell cycle, and in all age groups. Correlate intracellular PK parameters with drug efficacy and toxicity.
  - Develop novel and improved tools for drug discovery and the investigation of drug efficacy.
  - Develop novel and improved tools and systems biology approaches to better understand viral pathogenesis and drug PK in various intracellular and extracellular compartments.
  - Develop novel delivery systems that target specific tissues, cells, organelles, proteins, and nucleic acids.
  - Develop agents and strategies to improve biopharmaceutical characteristics (e.g., bioavailability, tissue penetration, and long-acting formulation).
  - Develop long-acting formulations to improve adherence and achieve drug concentration.

  - Develop enhanced ways to measure and monitor drug adherence and barriers to adherence to antiretroviral therapy (ART).
  - Develop drug delivery devices or systems that improve the PK profile of therapeutic agents, target specific organs or tissues, reduce toxicities and adverse effects, and result in improved adherence to therapeutic regimens.
  - Develop novel agents, taking into account that patients need to be on treatment for an extended time.

- Develop novel bioimaging applications to evaluate viral transmission and reservoirs, immune induction and modulation, and drug transport and metabolism.

- Advance basic and applied gene-based strategies to treat HIV infection. Foster new approaches and technologies to optimize gene delivery that results in regulated and persistent gene expression. Optimize *ex vivo* gene delivery and advance new concepts, strategies, and vectors for direct *in vivo* delivery.

- Develop therapeutic strategies, including approaches to identify patients in the early stage of HIV infection, with emphasis on prevention of early T-cell depletion in the gastrointestinal tract.

- Study the mechanisms and implications of drug resistance and viral fitness; evaluate early markers and genotypic mutations that lead to resistance and cross-resistance.

- Develop and evaluate interventions aimed at reducing HIV-related immune activation, while also identifying critical pathways by which chronic immune activation leads to end-organ disease.

- Develop mathematical and computer models of HIV infection and therapeutic interventions that simulate and predict *in vivo* cost-effectiveness, efficacy, toxicity, and other outcomes of drug regimens and clinical trials, including generic therapies. Investigate the use of pharmacogenetics in identifying optimal therapies.

- Study the molecular basis of ARV drug toxicities and approaches to reducing these toxicities without loss of antiviral effect.

- Develop and perform the PK evaluation of fixed-dose combination formulations of approved ARV drugs, including doses appropriate for children and geriatric populations.

- Develop and evaluate pediatric drug formulations of available and new ARV drugs, with emphasis on low-dose dividable solid formulations appropriate for use in resource-limited settings, as well as liquid formulations.

- Develop therapeutic agents for the treatment of HIV/AIDS that do not interact with psychotropic medications, drugs of abuse, medications to treat drug abuse, or other drugs.

OBJECTIVE–B: Conduct Clinical Trials of Anti-HIV Treatments

Assess the short- and long-term efficacy and effectiveness of therapeutic agents and novel strategies against acute, established or latent, HIV infection, viral reservoirs, and transmission in treatment-naive and treatment-experienced HIV-infected individuals, across the lifespan, through the conduct of clinical trials and cohort-based studies in domestic and international settings, especially in resource-limited nations; develop new clinical trial methodologies; and develop strategies to improve adherence and mitigate factors that adversely affect the success of therapeutic strategies against HIV infection. Develop domestic and international partnerships to design and conduct clinical studies where the epidemic is prevalent.

STRATEGIES

Clinical Trials of Therapeutic Agents

- Conduct clinical trials of potential therapeutic agents and combinations of agents in adults, including pregnant women and older populations, adolescents, children, infants, and other high-risk populations to determine PK, tissue bioavailability, antiviral activity, effects on the immune system, safety, and clinical efficacy.
  - Evaluate novel combinations of agents selected for maximizing antiviral synergy, complementary mechanism of action, minimal toxicity and cross-resistance, simplicity of administration, and tolerability.
  - Evaluate optimal therapies and novel strategies for individuals who have acute or recent infection (including neonates/young infants with perinatal infection), chronic infection but no prior ART, and those with prior ART, including individuals with multidrug-resistant virus.
  - Conduct clinical trials to study:
    - Long-term effectiveness (including toxicities) of novel therapeutic strategies;
    - Timing, selection, and strategic sequencing of ARV agents to optimize clinical outcome in relevant populations;
    - Simplified and maintenance regimens;
    - Optimal treatment for heavily ARV-experienced individuals with treatment failure;
    - Interaction of the effects of ART on HIV-related comorbidities;
    - Gender-based and genetic differences in special populations;
    - Evaluation of interventions to minimize ART-related comorbidities; and
    - ARVs and regimens that effectively inhibit virus replication in the central nervous system (CNS) and other sites that may be difficult to penetrate.
  - Conduct small clinical studies to validate potential new targets and/or explore novel therapeutics (e.g., cell-based and gene-based).
  - Evaluate coformulated and long-acting ARVs in all age groups.
  - Investigate the effects of class-sparing regimens on efficacy, resistance, and transmission.
  - Evaluate novel approaches and treatment regimens to prevent and eradicate viral reservoirs that may lead to a cure for HIV disease, including perinatally acquired infection.

Clinical Trials Enrollment

- Strengthen efforts and implement new approaches and in novel locations to ensure the enrollment and retention of specific populations, including women, children, adolescents, minorities, substance abusers, men who have sex with men, older adults, and marginalized high-risk populations in clinical trials and cohort-based studies to reflect the incidence of the epidemic.
- Strengthen efforts to evaluate new and existing drug treatment regimens in clinical trials and cohort-based studies that reflect the demographics of the epidemic. When appropriate, evaluate potential gender, race, ethnicity, age-specific, pregnancy-related, and nutrition-related differences in drug efficacy and safety, including PK, metabolism, tissue absorption, and drug elimination.

Clinical Trial Methodology

- Develop and evaluate standardized virologic, immunologic, and clinical markers to assess drug activity; determine and validate surrogate markers in response to various therapeutic interventions, including those most applicable to resource-limited settings.
- Develop novel inexpensive and rapid platforms, as well as point-of-care assay systems, for detection and quantification of HIV, diagnosis of recent HIV infection, ARV resistance testing, CD4 cell count, and adherence to therapy, biomarker evaluation, and genetic testing for both *in vitro* and *in vivo* evaluations.
- Develop, incorporate, and validate appropriate quality-of-life parameters and patient-reported outcome instruments in clinical trials of ARV agents.
- Develop methodologies to facilitate creative statistical analyses that will enhance the understanding of clinical trial outcomes.
- Develop methods to enhance the quality of trial conduct, including improved rates of enrollment, adherence, retention, and currentness of followup.
- Conduct studies on behavioral factors and prevention approaches that are critical to optimizing ART.
- Develop and test novel approaches to evaluate salvage therapy.
- Develop a framework to conduct clinical trials through research on bioethics.
- Develop novel approaches to expedite the development and conduct of clinical trials of anti-HIV treatments.
- Implement an informed consent process that permits patients' samples to be used for future clinical studies.

Pharmacology

- Determine the relationship between drug exposure, PK, pharmacogenomics, and outcomes (antiviral effect, immune function, and safety) to facilitate dosing strategies within clinical trials, as well as for individual patient management, including the utility of therapeutic drug monitoring and potential application of pharmacogenetics and the optimization of clinical trial design through clinical trial simulation.
- Investigate drug interactions, including PK and PD impacts, among commonly used treatments for HIV-related disease and its comorbidities, including medications taken by older individuals for pre-existing conditions, as well as other substances that may be used by HIV-infected individuals.
- Evaluate the effects of other host factors, including dietary intake and nutritional status, on the PK and activity of ARVs.
- Evaluate and optimize tissue penetration and concentration of ARVs.

Viral Reservoirs

- Quantitate persistent HIV in different tissue compartments during effective ART, and evaluate strategies to reduce or eradicate such reservoirs.
- Evaluate the penetration of ARVs into different body fluids and tissue compartments.
- Establish methodologies for accurate measurement of viral reservoirs.
- Develop more sensitive and less complicated tests for resistance.

Viral Resistance and Fitness

- Explore the utility of real-time ARV phenotypic and genotypic assays in managing ART across a broad spectrum of individuals.
- Evaluate the impact of transmission of drug-resistant strains of HIV on disease progression or response to therapy.
- Evaluate mechanisms to reduce the transmission of resistant virus.

Mechanisms of Treatment Success/Failure

- Investigate the viral and host factors associated with ART success/failure, including human genomics, drug interactions, drug resistance, drug toxicities, pharmacogenetics, malabsorption, and suboptimal adherence.

Adherence

- Support research on the effectiveness of pharmacological approaches, behavioral interventions, and other approaches to improve adherence to ARV regimens and retention in care.
- Develop improved methods to assess and enhance adherence to treatment regimens across a variety of affected populations; compare and validate adherence measures in the context of HIV treatment.
- Investigate strategies for managing symptoms that are attributed to therapy, and investigate the relationship between symptom management and improved adherence to ARV regimens.

International

- Expand the development of international collaborations to assist in addressing relevant therapeutic research in populations of HIV-infected adults, adolescents, and children, including studies on factors resulting in early deaths occurring within the first 3 months of treatment/care.
- Assist and encourage resource-limited nations, as appropriate, in technology transfer through training in the United States and on-site in-country, infrastructure, and capacity building to facilitate the evaluation of ARV agents and other therapies in local settings.
- Assess the barriers to delivery of effective health care for HIV disease, including treatment and the capability of conducting international therapeutic clinical trials through the establishment or expansion of multidisciplinary clinical centers.
- Develop standardized clinical indicators to determine how and when to initiate ART, to monitor responses to therapy, and to determine when to change therapy.
- Determine acceptable and practical laboratory monitoring methods for drug toxicity in resource-limited settings.
- Evaluate whether nutritional status (particularly chronic malnutrition) affects the efficacy of therapy and whether it affects the risk or severity of adverse events associated with ART.
- Evaluate ARV safety in pregnancy and lactation for mothers and their infants in resource-limited settings (e.g., prematurity, congenital abnormalities, breast milk ARV penetration, and infant toxicity).

OBJECTIVE–C: Approaches To Manage Consequences of HIV Infection and Its Treatment

Develop strategies to predict, evaluate, treat, and prevent complications of long-term HIV disease and toxicities of ART, and to investigate the role inflammation plays in these complications and comorbidities in HIV infection in domestic and international settings.

STRATEGIES

- Develop and evaluate therapeutic strategies for preventing and treating complications of HIV infection or its treatment.
- Evaluate potential delayed or late effects of ART following short-term administration of prophylactic regimens (e.g., for prevention of mother-to-child transmission [PMTCT]) or chronic drug administration.
- Develop standards that allow better comparison of late complications across clinical trials (i.e., meta-analysis between studies, efficacy of interventions in clinical trials versus effectiveness in public health practice).
- Support research on the pathogenesis and mechanisms of toxicity of drugs used to treat HIV disease.
- Develop and test approaches to prevent, reverse, or reduce potential metabolic abnormalities (e.g., changes in body composition, development of atherogenicity and endocrine disorders, and changes in bone and muscle structure and growth) based on an understanding of the mechanisms by which ART and/or HIV disease may affect metabolic processes.
- Develop and validate early markers of renal, liver, CNS, bone, cardiovascular, and other complications of ART and/or long-term survival with HIV disease.
- Integrate metabolic, endocrine, cardiovascular, neurologic, renal, liver, and musculoskeletal studies, including symptoms and symptom clusters, into ongoing and planned clinical studies, which may provide an opportunity to answer important questions related to HIV disease and the potential complications of ART. Conduct integrative multidisciplinary research for the management of medical complications associated with multiple infections of HIV, coinfections, and comorbidities, including addiction and mental disorders.
- Study the effects of gender, race, age, pregnancy and lactation status, and type of exposure on complications of ART.
- Evaluate the impact of nutritional status, impaired access to safe drinking water, regionally significant coinfections, and other population- and area-specific factors on complications of ART.
- Evaluate whether nutrition and nutritional interventions, provided concurrently with ART, improve clinical outcomes in HIV-infected patients, including lactating mothers.
- Evaluate drug interactions with potential clinical significance for HIV-infected individuals, particularly the PK and PD between ARVs and drugs used to treat HIV-related comorbidities or medications used in the treatment of drug addiction and mental disorders. Develop strategies to avoid or minimize the clinical impact of these interactions across all populations.
- In the context of clinical trials, study the effects of treatment and long-term HIV disease on the natural aging process and vice versa, including development of comorbidities across the lifespan of the HIV-infected individual.
- Define the pathogenesis of chronic inflammation in patients fully suppressed with ART.
- Evaluate approaches to prevent and treat immune activation, inflammation, and/or immune senescence associated with HIV disease and treatment.
- Evaluate the pathogenesis, diagnosis, and treatment of immune reconstitution inflammatory syndrome associated with the unmasking or paradoxical worsening of opportunistic infections following initiation of ART.

- Develop novel tools (including nanotechnology, proteomics, metabolomics, and immunotechnology) for rapid DNA sequence identification to facilitate toxicogenomic research and applications.

- Conduct research to evaluate biomarkers that predict end-organ disease.

OBJECTIVE–D: Prevent and Treat Coinfections

Develop and evaluate new agents and strategies for diagnosis, prevention, and treatment of the most significant coinfections for use in the context of HIV disease in domestic and international settings and across the lifespan of HIV-infected individuals, including but not limited to tuberculosis (TB), malaria, hepatitis C virus (HCV), hepatitis B virus (HBV), and Kaposi's sarcoma-associated herpesvirus (KSHV). Develop and evaluate new therapeutic agents and strategies to prevent and treat drug-resistant coinfections, particularly TB.

STRATEGIES

Preclinical Discovery and Development

- Support appropriate drug development programs to develop therapies against HIV-associated pathogens and their disease manifestations, especially *Mycobacterium tuberculosis* (TB) (including multidrug-resistant TB [MDR-TB] and extensively drug-resistant TB [XDR-TB]), malaria, HCV, HBV, human papillomavirus (HPV), KSHV/human herpesvirus (KSHV/HHV-8), cryptococcal infection, Epstein-Barr virus (EBV), and cytomegalovirus, with emphasis on innovative approaches and agents with favorable bioavailability and PK, as well as development of formulations appropriate for use in children.
- Utilize mechanism-based screening of novel synthetic compounds and natural products to identify candidate agents for treating the most significant coinfections; provide support for medicinal chemistry, structural databases, and toxicity testing.
- Support studies and develop vaccines and interventions for coinfections (e.g., TB, HPV, rotavirus) in HIV-exposed and HIV-infected individuals and other high-risk populations.
- Develop novel platforms for fast, accurate, and cost-effective detection and diagnosis of pathogenic organisms and related biomarkers.
- Develop novel delivery methods to both enhance the efficacy and decrease the toxicity of current and future therapeutic agents.
- Develop nano- and chemical-biology targeting modalities to selectively infiltrate and treat infected compartments, tissues, and cells.

Clinical Trials of Preventive and Therapeutic Regimens

- Assess the impact of new ARV regimens on the risks for and manifestations of infections associated with HIV disease.
- Improve understanding of the interplay between HIV-associated immune deficiencies and the onset and types of infectious complications.
- Improve strategies to prevent multiple infections in the context of ART; determine the optimal timing for initiating or discontinuing prophylaxis for different coinfections, particularly in resource-limited countries; develop improved strategies to minimize toxicities and the development of drug-resistant microorganisms.
- Support clinical trials of preventive and therapeutic regimens for HIV-related coinfections.
- Investigate the effects of maternal immunization for coinfections on pregnant women and on their infants.

Detection of HIV Coinfections

- Develop clinically useful assays and methodologies for early and rapid diagnosis of coinfections (particularly TB) and febrile illnesses, quantitative assessment of microbiological responses, and drug sensitivity testing, including assays appropriate for use in children with coinfections.

- Develop tools to identify HIV-infected individuals at high risk for development of specific coinfections, to improve the efficiency of clinical trial design and the risk–benefit ratio of the currently utilized drugs for prophylaxis and treatment.

Coinfections

- Study the interaction between HIV infection and infectious complications on pathogenesis, presentation, and disease outcomes.
- Develop models for studying biological interactions between HIV and coinfections to accelerate development of improved treatments.
- Support clinical trials, domestic and international, of adults and children coinfected with HIV and TB (both active and latent infection). Evaluate the safety and efficacy of treatment regimens in monoinfected, as appropriate, and coinfected individuals. Determine optimal length of treatment. Evaluate regimens in the context of degree of immunosuppression.
- Investigate surrogate markers of TB disease capable of distinguishing between latent, active, and eradicated infection in coinfected individuals; determine how each infection influences or alters the other disease in respect to progression and response to therapy.
- Conduct clinical trials investigating the efficacy and risks of treatment of coinfections including HBV, HCV, malaria, HPV, and TB in individuals who are coinfected with HIV; determine how each infection influences the other disease in respect to progression and response to therapy.
- Study the interaction of coinfections with HIV transmission (e.g., placental malaria and perinatal infections) and effects on HIV disease progression.
- Investigate the role of HIV-associated coinfections with pregnancy outcomes.
- Develop and evaluate biomarkers for HIV coinfections.

Pharmacology and Toxicology

- Conduct preclinical studies of anti-coinfection drugs (alone or in partnership with industry) to assess their immunologic, PK, PD, toxic, reproductive, and teratogenic effects, as well as transplacental carcinogenicity; develop pediatric formulations of anti-coinfection drugs, including lower-dose solid as well as liquid preparations.
- Support clinical studies to evaluate the safety and PK of existing and experimental agents intended to treat or prevent coinfections in HIV-infected infants, children, and pregnant women.
- Evaluate drug interactions between anti-TB agents and HIV medications. Support the investigation of new anti-TB agents with fewer side effects, drug interactions, and/or action against MDR- and XDR-TB.
- Support research on the interactions between ART and treatments for coinfections, including anti-HCV drugs, with special focus on PK/PD, mechanisms for interactions, and intracellular interactions.

Adherence and Self-Management

- Support research on the effectiveness of pharmacologic and other approaches in promoting adherence to anti-coinfection regimens.
- Develop formulations, routes of administration, and delivery systems for existing and experimental anti-coinfection drugs appropriate for use in infants, children, and other populations.
- Develop and evaluate interventions that improve adherence to therapies among HIV-infected individuals with co-occurring substance abuse and/or mental illness.
- Investigate strategies for managing symptoms that are attributed to HIV infection, coinfection, and/or therapy, and investigate the relationship between symptom management and improved adherence to ARV regimens. This may include self-management or combined biobehavioral approaches.

International

- Conduct clinical trials in adults (including pregnant women) and children to evaluate agents for the prophylaxis and treatment of HIV-associated coinfections; target infections shown to cause significant morbidity by epidemiologic studies, and made worse by HIV-induced immunosuppression.
- Develop and evaluate strategies for treatment and prevention of prevalent opportunistic and endemic infections in the context of HIV infection.
- Evaluate the role of nutrition, malnutrition, and severe malnutrition on treatment and prophylaxis regimens for coinfections.

OBJECTIVE–E: Treatment of AIDS-Related Neurologic Disease

Develop strategies for assessing, preventing, and treating HIV nervous system infection and central and peripheral nervous system manifestations of HIV disease in domestic and international settings.

STRATEGIES

Preclinical Development

- Develop therapeutic agents to block HIV entry into the CNS and treat HIV infection in the CNS; develop and evaluate novel strategies such as neuroprotective agents that are active against putative pathways of HIV-induced CNS dysfunction in adults, adolescents, and children.
- Optimize and utilize *in vitro, ex vivo,* and animal models of CNS lentivirus infections and CNS injury to identify therapeutic agents (tailored for needs during neurodevelopmental and mature brain periods) for the nervous system complications of HIV infection.
- Assess the pathogenic role of viral sequestration in the CNS, including its potential role as a reservoir of viral persistence and as a site of independent selection of antiviral drug-resistant strains and other mutants.
- Evaluate strategies to reduce or eliminate HIV reservoirs in the CNS.
- Assess the interactions between chronic HIV infection, HIV-associated neurocognitive disorders, and aging-related neurodegenerative disease.
- Assess CNS toxicity of novel eradication approaches.
- Develop objective quantitative assessments (e.g., surrogate markers in cerebrospinal fluid [CSF] and neuroimaging) of HIV disease progression and treatment effects as they relate to the nervous system.
- Characterize the CNS PK and PD of ARVs; determine the importance of CNS drug penetration, particularly penetration of the blood–brain barrier, in reducing CNS infection in neurologically symptomatic and asymptomatic subjects.
- Develop novel bioimaging applications and bioassays to facilitate assessment of compartmental PK/PD.
- Develop strategies for manipulating drug transporters at the blood–brain barrier to facilitate entry of ARVs into the CNS compartment.
- Develop novel tools (e.g., nanotechnology) to facilitate and modulate delivery of ARVs, neuroprotective agents, and agents that reactivate virus for eradication into the CNS compartment.
- Develop better strategies, including complementary and alternative medicine approaches, to prevent, diagnose, and treat peripheral neuropathies and other CNS complications in HIV-infected individuals.
- Develop optimal therapies for pain management in HIV-infected individuals.
- Monitor CSF for HIV viral load and immune activation markers in individuals enrolled in studies of ART and CNS eradication trials.
- Further elucidate the correlation among CSF HIV viral load, chemokine levels, proinflammatory cytokines, and markers of immune activation with CNS disease.
- Conduct studies on the effectiveness of approaches to facilitate better adherence to therapeutic regimens in neurologically impaired individuals.
- Evaluate the effectiveness of reducing HIV-associated CNS disease burden by therapeutic agents currently used to treat other neurologic diseases (e.g., Parkinson's and Alzheimer's disease) that may share pathophysiologic features with HIV-associated neurologic disease.
- Assess the incidence and prevalence of neurological and neurobehavioral complications, and assess the impact of other viral, bacterial, fungal, or parasitic infections on HIV disease in the CNS.

- Assess the impact of HIV clade diversity, the generation of HIV variants, and changes in virus tropism on neuropathogenesis and response to therapy.
- Determine anatomical, structural, and genetic contributors (e.g., haplotypes and epigenetics) to neurological vulnerability to HIV infection and related inflammatory processes.
- Conduct studies to determine drug interactions between commonly used treatments for HIV disease and its complications and treatments for drug abuse and co-occurring mental health disorders; develop treatments and regimens that are optimized for HIV-infected individuals with comorbid depression and other psychiatric disorders.
- Develop adjunctive therapeutic agents with both immunomodulatory and neuroprotective functions to reduce comorbid psychiatric conditions (markedly, depression and anxiety disorders) in HIV-infected individuals.
- Develop novel or adapt existing rehabilitative strategies to ameliorate HIV-associated CNS disease manifestations that affect social–emotional, motor, sensory, cognitive, and daily functioning.

Clinical Neuroassessment, Methodologies, and Trials

- Design and support clinical trials addressing nervous system complications of HIV infection and treatments across the lifespan.
- Design and support clinical trials for eradication of HIV from persistent CNS reservoirs.
- Improve existing and develop novel sensitive, reliable, and valid measures of neuropsychological performance and neuropsychiatric status having cross-cultural and international applicability and sensitivity to HIV-associated neurological complications and ARV treatment, including appropriate and standardized measures of neurodevelopment in children applicable to resource-limited settings.
- Identify and validate biomarkers to compare HIV-associated neurological disorders with other cognitive disorders.
- Determine the incidence and prevalence of HIV-associated neurocognitive disorders, primarily HIV-associated dementia, minor neurocognitive disorders, asymptomatic neurocognitive impairment, and peripheral neuropathy, in the context of long-term ART.
- Determine the type and timing of ART on neurodevelopmental function in HIV-infected children.
- Develop new statistical methodologies, clinical trial designs, and selection and investigation of biologic markers to evaluate the safety and clinical efficacy of new agents and approaches in the treatment of neurologic and cognitive complications of HIV disease.
- Develop, incorporate, and validate functional neurologic and quality-of-life scales in clinical trials and cohorts that are aimed at measuring the impact of nervous system complications of HIV infection.

OBJECTIVE–F: Assessment, Prevention, and Treatment of HIV-Related Cancers

Develop and evaluate improved strategies for the assessment, treatment, and prevention of cancer as a comorbidity of HIV disease in domestic and international settings.

STRATEGIES

Preclinical Development

- Promote screening, discovery, and development of novel therapeutic agents with activity against AIDS-defining and/or HIV-associated malignancies, including pathogenesis-based strategies, agents with optimal CNS penetration, agents with optimal safety profiles, and agents that are optimal in resource-limited settings.
- Promote discovery of drug enhancement and targeting modalities for malignancy-specific delivery of therapeutic agents.
- Develop agents utilizing structural, biologic, immunologic, and biochemical information for the prevention and treatment of HIV-associated malignancies.
- Develop preclinical and *in vivo* models for testing potential therapeutic and preventive strategies against HIV-associated malignancies.
- Utilize emerging information on the pathogenesis of malignancy complications of HIV infection, including new viral agents and the role of inflammation, to develop new preventive, diagnostic, and therapeutic strategies for such tumors, including vaccination strategies.
- Evaluate the role of inflammation as an accelerator for the development of malignancies.

Diagnostic Methods

- Develop and improve methods for early diagnosis of malignancies and premalignancies in the context of HIV disease and for early detection of recurrent cancer or secondary malignancies in adults and children.

Clinical Evaluation of Therapeutic and Prevention Strategies

- Develop therapeutic and prevention strategies (including vaccines) for AIDS-defining and other HIV-associated malignancies based on an improved understanding of the role of infectious agents (e.g., KSHV/HHV-8, EBV, HPV, HCV, Merkel cell virus, and HBV) in their pathogenesis.
- Conduct studies on the efficacy of HPV vaccines to prevent and treat HPV-induced cervical, anal, and oral cancer in HIV-infected populations, including adolescents.
- Evaluate novel approaches for the treatment of AIDS-defining and other HIV-associated malignancies through clinical trials, and evaluate the interactions between treatment of malignancies and treatment of the underlying HIV infection.
- Evaluate approaches using gene- and protein-based technologies, such as tissue array, microarray, and whole genome sequencing, in targeting treatment of AIDS-defining and other HIV-associated malignancies.
- Conduct research to assess the optimum therapy for cancers in HIV-infected individuals, including elderly patients.
- Develop, incorporate, and validate clinical trial methodologies to correlate tumor-specific responses in HIV-infected individuals with clinical benefit, including quality-of-life parameters; develop staging systems indicative of prognostic response and survival.
- Identify surrogate endpoints indicative of response to therapy and novel methods for evaluating tumor response in HIV-infected individuals, including imaging technology.

- Encourage and facilitate collaborative studies within clinical trials networks to develop mechanisms for early identification of individuals at high risk for AIDS-defining and other HIV-related malignancies. Develop and assess interventional strategies to reduce the risk or prevent the development of AIDS-related malignancies, such as interventions in the premalignant stages.

- Study the role of immunomodulating agents in the treatment and prevention of AIDS-defining and other HIV-related tumors.

- Support clinical studies of HIV-infected individuals with non-AIDS-defining malignancies in order to define the best treatment of these malignancies. Evaluate the impact of cancer therapy on virologic, immunologic, and tumor parameters, including viral reservoirs; assess the toxicity of anticancer modalities in HIV-infected patients; evaluate the PK of anticancer agents in HIV-infected patients, including a study of drug–drug interactions; and assess the utility of cancer therapies, including bone marrow transplantation, in the eradication of HIV infection in HIV-infected patients.

- Explore strategies for attenuating or preventing toxicities associated with anticancer therapy in HIV-infected patients, and study the effects of such strategies on virologic and immunologic parameters in HIV-infected individuals.

- Study the role of *in utero* and long-term exposure to ARVs on the risk of later development of tumors.

- Develop and assess preventive, diagnostic, and therapeutic strategies that are appropriate in resource-limited settings for AIDS-defining and other HIV-related malignancies, especially those due to endemic infectious agents (e.g., KSHV/HHV-8), EBV, and HPV).

OBJECTIVE–G: Immune Reconstitution Approaches

Develop and assess therapeutic approaches that will restore, sustain, and enhance a competent immune system in HIV-infected individuals in domestic and international settings.

STRATEGIES

- Develop and evaluate approaches to enhance immune restoration in clinical trials; test specific hypotheses of HIV immunopathogenesis.
- Evaluate the capacity of the immune system to maintain or repair itself after maximal effective viral suppression, considering the effects of gender, race/ethnicity, and age.
- Evaluate strategies to improve HIV-specific immunity, especially in patients on successful long-term therapy.
- Develop, validate, and standardize new methods for evaluating immune function in clinical trials that enroll adults, adolescents, and children, including assays that may be used in resource-limited settings.
- Accelerate the preclinical and clinical testing of cytokines, modulators of cytokines, combinations of broad-based neutralizing monoclonal antibodies, and immunoactive agents to prevent further immune deterioration, to reconstitute deficient immune systems, and to enhance the immunogenicity of therapeutic HIV vaccines.
- Develop optimal active and passive immunotherapeutic approaches (including therapeutic vaccine candidates) for HIV infection and its sequelae, including the testing of immunogens and adjuvants; determine optimal patient disease status for response, most effective immunization dose and schedule, and most meaningful readout of clinical impact of the intervention.
- Support research on approaches to facilitate better adherence to immunoactive regimens.
- Evaluate the safety and efficacy of administering cellular immune elements, including use of expanded and/or modified peripheral blood T cells, bone marrow, cord blood stem cell transplantation, stem cell therapy, and thymic transplantation, for restoration of the immune system and viral eradication.
- Evaluate the immune system after partial restoration by ART. Define differences between the restored immune system and the naive immune system to determine if identified deficiencies can be diminished by immunoactive agents, including the use of vaccines for specific opportunistic infections and coinfections.
- Develop new therapeutic strategies based on gene delivery strategies to protect mature, hematopoietic stem cells, hematopoietic pluripotent cells, and stromal cell elements from destruction by HIV.
- Study the mechanisms of action of immunomodulating agents, and proceed with applied studies and development of the most promising approaches.
- Evaluate immune-based therapy as an adjunct to salvage therapy strategies and/or reservoir elimination.
- Identify immunological predictors of *in vivo* immune control of viral replication.

OBJECTIVE–H: Management of HIV Disease With Nonpharmacologic and Complementary and Alternative Modalities

Develop and assess novel interventions (e.g., nonpharmacologic complementary and alternative medicine) for the prevention and symptom management of HIV disease and its complications, including those prevalent in, or unique to, international settings.

STRATEGIES

- Develop and evaluate conventional and nonconventional chemopreventive approaches, including those containing quantifiable doses of micronutrients (such as vitamins and trace elements) and macronutrients to delay the development of wasting and other HIV-associated manifestations.
- Evaluate the safety and efficacy of nonpharmacologic and complementary and alternative medicine approaches, such as exercise, nutrition, and sleep cycles, in the management of HIV disease and its associated manifestations.
- Evaluate the benefits or risks and PK interactions of commonly used complementary agents (herbal, homeopathic, and/or naturopathic) when used concomitantly with ART.
- Determine the role of traditional healers and the impact of the use of traditional medicines, herbal medicines, and supplements on HIV treatment and care, and nonstandard use of ART that can lead to resistance.

AREA OF EMPHASIS

Research Toward a Cure

FY 2015 RESEARCH PRIORITIES

- Further the understanding of fundamental viral and host mechanisms associated with the control and persistence of HIV at the cellular, tissue, and viral level, and identify the sites, mechanisms of persistence, and strategies for host molecular and/or immune containment and eradication of HIV reservoirs.

- Design and test novel approaches to eliminate viral reservoirs and persistent virus, as well as strategies to control viral pathogenesis.

- Identify and validate novel assays to measure the replication-competent viral reservoir. Evaluate the contribution of persistent HIV replication in the presence of effective antiretroviral therapy (ART). Develop and test animal and *in vitro* models that are predictive of HIV eradication.

- Assess knowledge, beliefs, and attitudes toward cure research and the possible scale-up of relevant eradication strategies and approaches.

OBJECTIVE–A: Biology of HIV Infection

Delineate the viral and host mechanisms involved in HIV infection, persistence, and dissemination, and the establishment and maintenance of the viral reservoir. Identify factors involved in the control of HIV disease progression and host restriction in the presence of ART in diverse populations across the spectrum of age, gender, and race and/or ethnicity in national and international settings.

STRATEGIES

Basic Research on the Establishment of Persistent HIV Infection

- Identify and validate viral and host cellular contributions required for HIV persistence that can be targeted for eradication of latent and persistent virus.
- Determine structural information on HIV and cell constituents involved in HIV infection that will inform future design of potent and selective therapeutic agents and therapeutic vaccine candidates needed for eradication.
- Determine the mechanisms by which host and virus-encoded genes or viral gene products regulate and influence establishment of HIV latency infection within specific cell populations and/or tissue compartments.
- Determine cellular or viral factors associated with transition from latent state to active replication.
- Assess the impact of transmission of drug-resistant strains of HIV on reservoir establishment, disease progression, or response to therapy.
- Examine the effect of route and duration of infection and of ART regimens on establishment, persistence, perturbation, and eradication of reservoirs.

HIV Replication and Viral Dissemination

- Determine whether ongoing viral replication occurs in individuals on fully suppressive ART regimens and the mechanisms responsible for ongoing replication.
- Characterize new and understudied viral and host targets, sequence of infection, and mechanisms of viral transfer important for the early dissemination of HIV *in vivo*.
- Evaluate the role and mechanisms of preventing or enhancing HIV replication and dissemination by soluble factors contained within bodily fluids.
- Investigate the role of immune activation, inflammation, immunosenescense, and their mediators in various tissues on the establishment and dissemination of HIV infection.
- Identify immunological predictors of immune control of viral replication.
- Delineate the mechanisms and impact of genetic or environmental factors on immune responses that influence HIV replication and dissemination to lymphoid and other tissues and reservoirs.

Latent and Persistent HIV Reservoirs

- Explore the role of innate and adaptive immunity in governing the size of the latent viral reservoir.
- Identify the tissue and cellular reservoirs of latent or persistent HIV.
- Determine whether latent virus infects and is maintained in non-T-cell populations and the contribution of cells of the monocyte lineage to the HIV reservoir.
- Define the role of different CD4+ T-cell subsets (central, transitional, and effector memory) in the establishment and persistence of latent reservoirs.

- Determine whether HIV clade differences and viral tropism play a role in establishing latent reservoirs.
- Determine the role of host genetics in the establishment and maintenance of latent reservoirs.
- Define sites and mechanisms of latent/persistent HIV infection in patients on suppressive therapy, and the mechanisms by which reservoirs are established and maintained in the presence of ART.
- Develop tools to measure and quantify HIV in reservoirs such as novel imaging techniques.
- Define the molecular mechanisms that lead to the initial establishment, subsequent maintenance, and reactivation of latently infected cells.
- Develop and evaluate novel mechanisms to eliminate HIV reservoirs or prevent viral reactivation in latently infected cells.
- Identify host or environmental factors that may alter the establishment and/or maintenance of tissue and cellular reservoirs.

Disease Progression and Pathogenesis

- Delineate the viral and host mechanisms responsible for the differences between pathogenic and nonpathogenic HIV/simian immunodeficiency virus (SIV) infection.
- Determine the correlates of immune control by studying HIV-infected individuals across the lifespan, and SIV or chimeric simian/human immunodeficiency virus nonhuman primate models.
- Explore mechanisms of host response to HIV or SIV infection that involve the interface between innate, mucosal, and adaptive immunity.
- Elucidate the mechanisms of CD4+ T-cell depletion in the infected host.
- Examine the role of immune dysfunction/dysregulation in HIV or SIV pathogenesis, and delineate the mechanisms leading to pathological immune activation and autoimmunity in HIV or SIV infection.
- Define the sites of infection and replication in the untreated host at the cellular and cell subset levels, both anatomically and functionally; and how cell subset targeting determines disease progression or non-progression.
- Identify the host immune responses to HIV-1, as well as the viral or host factors that enhance or reduce the amounts of circulating virus and influence disease course in long-term non-progressors and elite controllers.
- Delineate the mechanisms by which sexually transmitted infections, other coinfections, comorbidities, environmental factors, and the microbiome (bacterial, fungal, and viral) influence HIV replication and dissemination and contribute to HIV persistence.

Neurological Factors and Reservoirs

- Develop novel strategies to inhibit HIV spread in the central nervous system (CNS) during periods of release from persistently infected cells.
- Assess the pathogenic role of viral sequestration in the CNS, including its potential role as a reservoir of viral persistence and as a site of independent selection of antiviral drug-resistant strains and other mutants.
- Develop therapeutic agents to block HIV entry into the CNS and design novel tools (e.g., nanotechnology) to facilitate and modulate delivery of antiretrovirals (ARVs) and novel eradication agents into the CNS compartments to treat HIV infection.
- Determine the pharmacokinetics/pharmacodynamics (PK/PD) of ARVs in the CNS; determine the importance of CNS drug penetration, particularly penetration of the blood–brain barrier, in reducing CNS infection/reservoirs in neurologically symptomatic and asymptomatic individuals.

Methodology and Animal Models

- Develop cell-based models of the blood–brain barrier to test transport efficiencies of ARVs and transport of HIV into the CNS.
- Develop physiologically relevant *in vitro* and *ex vivo* organ or tissue systems and animal models that can be used to discover agents or approaches that target and eliminate HIV that persists in the presence of ART.
- Develop novel models to study key features of infection, pathogenesis, and latency.
- Develop novel tools and systems biology approaches to better understand viral persistence, pathogenesis, and drug PK in various intracellular and extracellular compartments.
- Develop novel bioimaging applications (including nanotechnology) and bioassays to evaluate viral reservoirs, immune induction and modulation, drug transport, metabolism PK, and PD in tissues that serve as potential viral reservoirs.
- Employ new technology, including computational biology, bioimaging, systems biology, stem cell technologies, and high-throughput technology, to advance the understanding of the earliest events in the establishment of foci of infection, latency, viral reactivation, and dissemination.
- Develop new statistical methodologies, quantitative assessments, clinical trial designs, and selection and investigation of biologic markers to evaluate the safety and clinical efficacy of new agents and approaches in the treatment of neurologic and cognitive complications of HIV disease targeting residual HIV infection in the CNS reservoir.
- Develop or improve sensitive quantitative measures of HIV or SIV in body fluids, including oral and genital secretions and breast milk, and tissue reservoirs, such as lymphatic tissue and the CNS, to assess the effectiveness of interventions designed to control or eradicate HIV infection.
- Coordinate the development of reagents and standardized methods to assess specific HIV or SIV eradication strategies *in vivo*.
- Support collaborative studies using genetic methods applied to diverse populations to elucidate mechanisms of susceptibility to HIV infection, control of disease progression, and related complications.

OBJECTIVE–B: Discover and Develop Strategies Targeted Toward a Cure for HIV/AIDS

Identify and validate viral and host cellular factors and functions that can be targeted for eradication of persistent virus. Discover and develop novel agents and virological, immunological, and cellular therapeutic strategies that are effective in eradicating HIV across the spectrum of age, gender, and race and/or ethnicity in national and international settings.

STRATEGIES

- Develop new agents and treatment strategies that target, inhibit, and clear HIV in cellular, anatomical, and organ reservoirs and sanctuaries, including agents that can suppress and clear HIV in non-T-cell reservoirs.
- Evaluate the intracellular PK and activity of ARVs in different tissue and cell types, different stages of the cell cycle, and across the lifespan. Correlate intracellular PK parameters with drug efficacy and toxicity.
- Develop agents and delivery systems to eradicate HIV with desirable biopharmaceutical characteristics (e.g., improved bioavailability; tissue penetration targeted to specific tissues, cells, organelles, proteins, and/or nucleic acids; reduced toxicities and adverse effects; and long-acting formulation) to facilitate uptake, adherence, and adherence monitoring.
- Advance gene-based strategies to protect cells subject to the cytopathic or cytotoxic effects of HIV infection.
- Determine the mechanisms of action of immunomodulating agents, and develop the most promising approaches alone or in combination with biopharmaceutical agents.
- Design, develop, produce, and preclinically test novel active and passive HIV therapeutic vaccine candidates for safety and for their ability to control or eliminate viral reservoirs.
- Develop and optimize the SIV/macaque model for studies of virus eradication in which the animals are treated with ART and then additional interventions are performed.

OBJECTIVE–C: Conduct Clinical Studies of Strategies Capable of Eradicating HIV

Assess the short- and long-term efficacy and effectiveness of therapeutic agents and novel strategies against acute, persistent, or latent HIV infection and viral reservoirs in HIV-infected individuals across the lifespan, including in older individuals, through the conduct of clinical studies across the spectrum of gender and race and/or ethnicity in national and international settings, especially in resource-constrained nations.

STRATEGIES

- Expand and improve on existing domestic and international partnerships to design and conduct clinical studies.
- Perform pilot studies of evidence-based potential therapeutic agents and combinations to determine proof of concept, validation of assay(s) and method(s), and tissue bioavailability in eradicating HIV reservoirs.
- Conduct clinical studies of potential therapeutic agents and combinations of strategies to determine safety and efficacy in diminishing or eliminating latent virus.
- Conduct clinical studies of potential therapeutic agents and combinations of strategies to determine whether ongoing viral replication is occurring in individuals with nondetectable virus while on ART.
- Conduct clinical trials to study long-term effectiveness (including toxicities) of novel therapeutic strategies to eradicate HIV.
- Evaluate coformulated and long-acting ARVs across the lifespan of the HIV-infected individual.
- Quantitate persistent HIV in different tissue compartments during effective ART, and evaluate strategies to reduce or eradicate such reservoirs.
- Improve methods to measure the penetration of ARVs and other agents into various body fluids and tissue compartments, including the cerebrospinal fluid as a surrogate marker for the CNS.
- Develop and assess therapeutic approaches that will restore, sustain, and enhance the immune system in HIV-infected individuals.
- Advance clinical testing of cytokines, modulators of chemokines, combinations of broad-based neutralizing monoclonal antibodies, and immunoactive agents to prevent further immune deterioration, to reconstitute deficient immune systems, and to enhance the immunogenicity of therapeutic HIV vaccines.
- Develop and evaluate active and passive immunotherapeutic approaches (including therapeutic vaccine candidates) for HIV infection and its sequelae, including the testing of optimum immunogens; determine optimal patient disease status for response, most effective immunization dose and schedule, and most meaningful readout of clinical impact of the intervention.
- Evaluate the immune system after partial restoration by ART. Define qualitative and quantitative differences between the restored immune system and the naive immune system to determine if identified deficiencies can be diminished by immunoactive agents.
- Assess immune-based therapy as an adjunct to salvage therapy strategies and/or reservoir elimination.
- Evaluate the extent to which HIV or SIV-related immunopathogenesis can be prevented or reversed by therapeutic interventions.
- Investigate the impact of cancer therapy, immunosuppressive agents, and other immunomodulatory and myeloablative therapy on virologic, immunologic, and tumor parameters, including viral reservoirs; assess the toxicity of anticancer modalities in HIV-infected patients; and evaluate the PK of anticancer agents in HIV-infected patients, including a study of drug–drug interactions.

- Investigate the mechanism by which graft-versus-host reaction contributes to reducing/eliminating latently infected host cells in the setting of allogeneic stem cell transplantation.

- Study the impact of early ART interventions and HIV therapeutic vaccines or passive antibodies administered while on effective ART on the maintenance or regeneration of naive T cells and antiviral immune responses in HIV-infected infants.

- Conduct Phase I, Phase II, and Phase III HIV evidence-based therapeutic vaccine clinical trials that will determine short- and long-term safety; immunologic responses measured by a broad range of humoral, cell-mediated, and mucosal immune parameters; and effects on inflammatory markers and reservoir size.

OBJECTIVE–D: Behavioral and Social Science Research

Support behavioral, social, structural, and environmental research to inform the development, testing, and implementation of HIV eradication and cure approaches, and to develop and test interventions to strengthen the reach and impact of HIV eradication and cure strategies across the spectrum of age, gender, and race and/or ethnicity in national and international settings.

STRATEGIES

- Conduct studies on psychosocial and ethical issues that may influence the willingness of patients, providers, and communities to participate in clinical trials for HIV eradication, including the acceptable levels of risks and benefits associated with HIV eradication in the context of effective treatment.
- Conduct studies to determine effective communication strategies for working with communities to accurately understand the risks and benefits of HIV eradication and cure research efforts.
- Develop methods to assess and enhance adherence in HIV eradication and cure research and clinical practice; closely monitor adherence to HIV eradication and cure strategies during clinical trials and examine the association between adherence and trial outcomes.
- Develop necessary and appropriate assessment tools to measure social and behavioral factors (e.g., risk perception, behavior, and stigma) that may change during the course of participation in HIV eradication research.
- Conduct assessments of social and behavioral factors during clinical trials of strategies to eradicate HIV to identify and evaluate any changes in those factors as a result of participation in a clinical trial.
- Conduct behavioral research with individuals who become reinfected during clinical trials to identify interventions that may prevent high-risk behaviors and nonadherence in future clinical studies.
- Conduct social and policy research to investigate potential health disparities associated with cure/eradication research and its implementation.

OBJECTIVE–E: Implementation Science

Establish research collaborations to advance HIV/AIDS cure research as well as translational research to enhance the uptake of strategies to eradicate HIV/AIDS across the spectrum of age, gender, and race and/or ethnicity in national and international settings.

STRATEGIES

- Develop, validate, and standardize simple, sensitive, reliable, user-friendly, and inexpensive surrogate markers, assay technologies, and rapid point-of-care diagnostics for monitoring HIV virologic status that can be used in resource-limited settings, including viral persistence and responses to therapeutic strategies, as well as HIV drug resistance and adherence to treatment.

- Develop, validate, and standardize new methods and/or instrumentation for evaluating immune function in clinical trials, including assays that may be used in resource-limited settings.

- Develop cost-effective approaches to foster the scale-up of safe and efficacious therapeutic regimens, therapeutic vaccines, and other strategies to eradicate HIV for broad domestic and international use.

- Participate in collaborative efforts with other U.S. and international partners (i.e., research organizations and philanthropic institutions) to expedite cure and eradication research and the dissemination and uptake of its findings.